Medical and Research Publications
International Open Access

Case Report **Journal of MAR Neurology (Volume 3 Issue 2)**

Menkes Disease – An Uncommon Cause of Infantile Neurodegeneration

Dr. Nikhil Pawar*, Dr. Samar Almuntaser[1], Dr. Gururaj Aithala[2], Dr. Fatima Farid Mir[3]

1.Dr. Samar Almuntaser, Pediatric Neurology Department, Latifa Women and Children Hospital, Dubai.

2.Dr. Gururaj Aithala, Pediatric Neurology Department, Latifa Women and Children Hospital, Dubai.

3.Dr. Fatima Farid Mir, General Pediatrics Department, Latifa Women and Children Hospital, Dubai.

Corresponding Author: Dr. Nikhil Pawar, Pediatric Neurology Department, Latifa Women and Children Hospital, Dubai.

Received Date: July 27, 2021

Published date: August 01, 2021

Abstract

A four-month-old, previously healthy boy presented with acute onset of prolonged, recurrent seizure activity followed by neurodevelopmental deterioration and concurrent hair shaft hypopigmentation with fragility. Initial evaluation revealed significant low serum copper and ceruloplasmin, electrical status epilepticus on Electroencephalography (EEG), and generalized sub-cortical white matter changes with diffuse tortuosity of intra- cranial vessels on MRI brain. In addition, a genetic study with whole-genome sequencing demonstrated a hemizygous pathogenic variant at c.2179G>A p. (Gly727Arg) on ATP7A, thereby confirming the diagnosis of Menkes Disease. Symptomatic treatment with antiepileptic medications was provided along with an urgent referral to an advanced center for multi-disciplinary care and copper histidine replacement therapy.

Introduction

Menkes Disease is a lethal neurodegenerative disorder due to defective ATP7A gene function. A perturbation in copper metabolism leads to failure of dependent cellular enzyme function and subsequent multi-system disease. The inheritance pattern is X-linked recessive; however, approximately one-third of affected males have a negative family history, **[**1**]** and recent studies have demonstrated carrier female disease phenotype **[**2**]**. Onset is in early infancy with relentless deterioration and an early demise by three years of age. Response to copper histidine is guarded and heavily dependent on the timing of therapy. We report a prototypal case of severe Menkes Disease with genetically proven ATP7A defect.

Case Report

A previously healthy four-month-old boy presented with a two-week history of prolonged and recurrent seizures.

The infant was a product of non-consanguineous marriage, delivered at term via normal vaginal delivery with a birth weight of 2.7 kg. The postnatal period is remarkable for neonatal sepsis, otherwise uneventful. Negative family history for seizures or developmental delay.

After routine four-month immunization, the infant developed epilepsy, neurodevelopmental deterioration, with concurrent hair fragility and hypopigmentation.

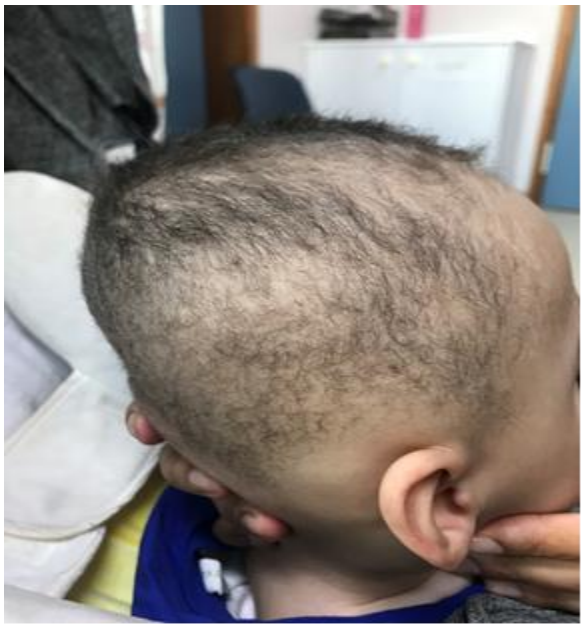

Figure 1: Short, coarse, hypo-pigmented, brittle and twisted hair.

Physical examination revealed normal head circumference and anterior fontanelle with frontal prominence and sparse, hypopigmented, kinky scalp hair [Figure 1]. Neurological examination showed visual inattention, mild axial and limb hypotonia, brisk reflexes without any neurocutaneous signs. Systemic examination was within normal limits.

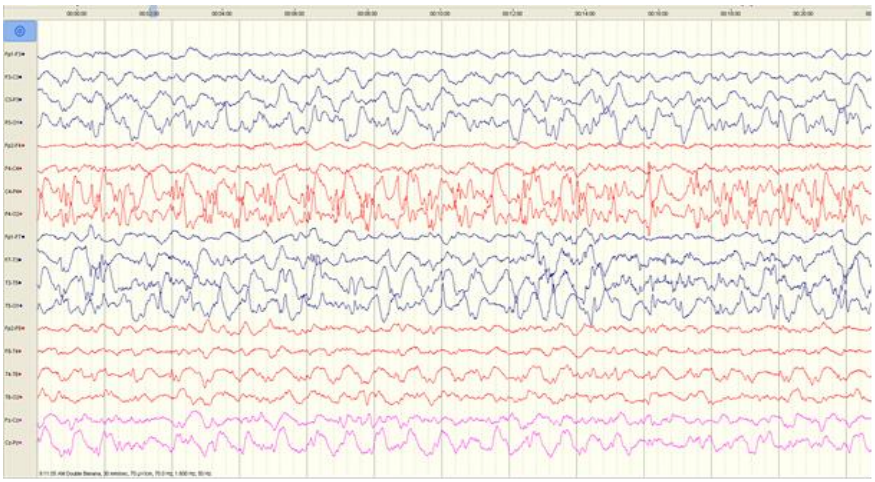

Figure 2: EEG showed features suggestive of electrical status epilepticus with bilateral centrotemporal epileptiform activities (more prominent on the right side).

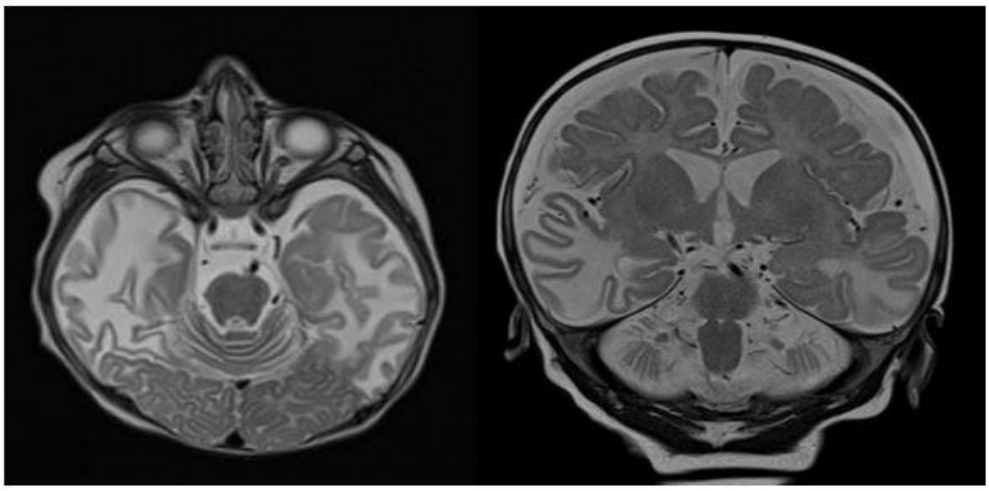

Figure 3: Diffuse subcortical white matter signal changes in the bilateral temporo- parietal regions suggestive of gliosis with hypo intense signal in T1 and FLAIR images with hyper- intense signal in T2 with no restricted diffusion or blooming artifacts.

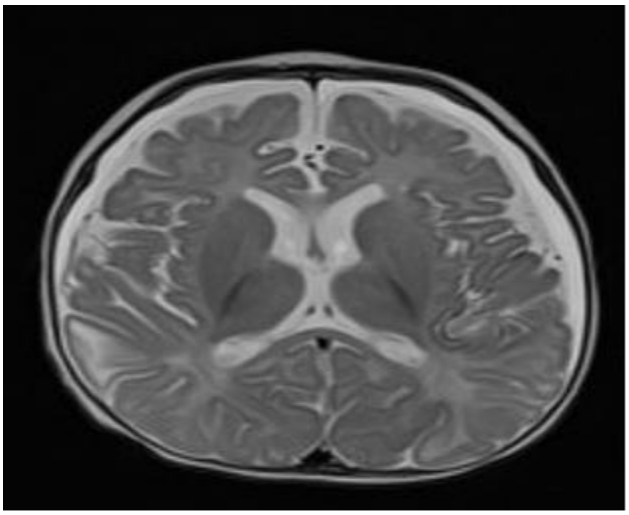

Figure 4: Cortical atrophy and Extra- axial hydrocephalus.

His prolonged complex seizure required admission and management with antiepileptic drugs (Levetiracetam and Topiramate). EEG showed features suggestive of electrical status epilepticus with bilateral centrotemporal epileptiform activities (more prominent on the right side) [Figure 2]. MRI brain revealed T2 hyperintensities of white matter in bilateral temporoparietal region suggestive of gliosis along with cortical atrophy, and extradural hydrocephalus [Figure 3-4]. With a clinical suspicion of a genetic metabolic defect, focused investigations were sought, and subsequent reports were highly suggestive of underlying Menkes Disease [Table 1]. The patient attained seizure freedom by six months of age; however, he relapsed once his mother tapered medications.

FBC	Normal
Urea electrolytes	Normal
Liver function test	Normal
Serum Copper	24 g/dL (Reference range 72-166)
Serum Ceruloplasmin	0.03 g/L (reference range: 0.15-0.62 g/L)
Blood Aminoacid chromatography	Normal
Amino acid acyl carnitine	Normal

Table 1

In light of the above, the child travelled abroad for genetic investigations. Whole-genome sequencing revealed a hemizygous pathogenic variant at c.2179G>A p. (Gly727Arg) on ATP7A while, the mother carried a novel pathogenic heterozygous variant c.2179G>A p.(Gly727Arg) in ATP7A gene, consistent with the diagnosis of Menkes Disease.

The Pediatric Neurologist reviewed the child; rehabilitation and home-based physiotherapy were recommended. Urgent referral made to center with higher specialization for multi-disciplinary care and copper histidine replacement therapy.

Discussion

Copper is an essential element involved in cellular health. It is the third most abundant element in the body after iron and zinc, and its delicate homeostasis is crucial for preserving normal bodily functions, particularly neurologic and connective tissues. **[**3**]** Among the two most well-recognized disorders of copper metabolism is Menkes Disease, arising due to copper deficiency, and Wilson Disease, a consequence of copper toxicity.

Menkes Disease holds an estimated prevalence of 1 in 8,664 live male births. **[**4**]** It is among a spectrum of disorders arising from defective ATP7A, the critical X-linked gene encoding copper transporting ATPase. The fundamental disease process is of a preserved cellular copper uptake but aberrancy in transportation and subsequent utilization by its dependent enzymes. **[**1, 3, 5**]**

Key examples of the latter include cytochrome c oxidase required for electron transport; superoxide dismutase responsible for free radical detoxification; dopamine beta-hydroxylase needed for catecholamine production; lysyl oxidase required for cross-linking of elastin and collagen; and peptidyl-glycine alpha amidating monooxygenase (PAM) needed for bioactivation of peptide hormones. **[**3**]**

There has been a demonstrated parallel between the degree of residual ATP7A activity and disease phenotype, which would explain the spectrum of disease presentation from mild Occipital Motor Horn Syndrome to lethal classical Menkes Disease. **[**6, 11**]** Recent reports have even demonstrated disease phenotype in carrier females (in addition to the rare occasions of sex chromosome aneuploidy or X-autosome translocation). **[**2**]**

Classic Menkes Disease typically manifests at six to eight weeks of age with progressive loss of developmental milestones, new onset of seizures, hypotonia, failure to thrive, and the concomitant onset of characteristic hair shaft anomalies (sparse, coarse, brittle, short, twisted hair with a microscopic picture of pili torti, monilethrix, trichorrhexis nodosa). **[**7- 10, 12, 16- 19**]** Diagnosis is hinged upon characteristic clinical features, lab findings of low serum copper and ceruloplasmin, EEG features of focal spikes with subsequent secondary generalization **[**20**]**, MRI brain evidence of vascular anomalies,

myelination delays and neurodegenerative changes **[**13- 15**]**, as well as absolute confirmation via genetic analysis. Disease prognosis remains poor, with most children dying by three years of age after respiratory tract infections.

Therapeutic modalities are limited to parenteral administration of copper histidine, which can ameliorate neurologic disease but cannot reverse the connective tissue manifestations. **[**1**]** Major confounding factors include timing of replacement therapy (negligible response if treatment delayed beyond) and ease of access to copper histidine therapy (both financially and geographically). Prenatal diagnosis is of utmost importance once a proband is diagnosed, as that would aid in early identification in the following offspring. **[**1, 16**]**

Conclusion

Menkes disease is a lethal neurodegenerative condition with onset in a previously well infant. Diagnosis hinges on astute clinical observation- the combination of pathognomonic hair shaft changes and neurodegeneration in a well-child should spark confirmation via investigations as available. Treatment is with parenteral copper histidine administration at the earliest time possible, along with general supportive management.

Statements

Acknowledgment: Nil

Statement of Ethics: We have written informed consent from the patient's parents for publishing the case report, including any accompanying materials.

Disclosure Statement: The authors have no conflicts of interest to declare.

Funding Sources: The authors have no funding sources to declare.

Author Contributions: All authors have contributed to writing, researching and finalizing the case report.

References

[1] Kaler SG, DiStasio AT. “ATP7A-Related Copper Transport Disorders”. 2003 May 9 [Updated 2021 Apr 15]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021.

[2] Desai V, Donsante A, Swoboda K, Martensen M, Thompson J, Kaler S. “Favorably skewed X-inactivation accounts for neurological sparing in female carriers of Menkes disease”. Clinical genetics 2011 Feb;79(2):176-182.

[3] Tümer Z, Horn N. “Menkes disease: recent advances and new aspects”. Journal of medical genetics 1997 Apr;34(4):265-274.

[4] Kaler SG, Ferreira CR, Yam LS. “Estimated birth prevalence of Menkes disease and ATP7A-related disorders based on the Genome Aggregation Database (gnomAD)”. Molecular genetics and metabolism reports 2020 Sep;24:100602.

[5] Kodama H, Fujisawa C, Bhadhprasit W. “Inherited Copper Transport Disorders: Biochemical Mechanisms, Diagnosis, and Treatment”. Current drug metabolism 2012 Mar;13(3):237-250.

[6] Kaler SG, Holmes CS, MT, Goldstein DS, Tang J, Godwin SC, et al. “Neonatal Diagnosis and Treatment of Menkes Disease Abstract”. Engl J Med 2008;358:605.

[7] Fister P, Rakus J, Primec ZR, Strazisar BG. “Menkes kinky hair disease (Menkes syndrome). A case report”. Acta dermatovenerologica Alpina, Panonica, et Adriatica 2006 Sep;15(3):126-130.

[8] Verma A, Menghani K, Sureka B, Mittal A, Bhatt S. “Menkes Kinky Hair Disease Clinical Radiology for Pediatricians”. INDIAN PEDIATRICS 2016;86.

[9] Hussain DAA. “Menkes Syndrome: A Case Report”. Journal of medical science and clinical research 2018 Apr 30,;6(4).

[10] BOCOPOULOU F, HENDERSON L, PHILIP SG. “Menkes disease mimicking non-accidental injury”. Archives of disease in childhood 2006;91(11):919.

[11] León-García G, Santana A, Villegas-Sepúlveda N, Pérez-González C, Henrríquez-Esquíroz JM, de León-García C, et al. “The T1048I mutation in ATP7A gene causes an unusual Menkes disease presentation”. BMC pediatrics 2012 Sep 19,;12(1):150.

[12] Datta AK, Ghosh T, Nayak K, Ghosh M. “Menkes kinky hair disease: a case report”. Cases journal 2008 Sep 18;1(1):158.

[13] Manara R, D' Agata L, Rocco MC, Cusmai R, Freri E, Pinelli L, et al. “Neuroimaging Changes in Menkes Disease, Part 1”. American journal of neuroradiology: AJNR 2017 Oct;38(10):1850-1857.

[14] Manara R, Rocco MC, D'agata L, Cusmai R, Freri E, Giordano L, et al. “Neuroimaging changes in Menkes disease, part 2”. American journal of neuroradiology: AJNR 2017 Oct;38(10):1858-1865.

[15] Rangarh P, Kohli N. “New Menkes Disease Findings from King George's Medical University Described (Neuroimaging findings in Menkes disease: a rare neurodegenerative disorder)”. Obesity, fitness, & wellness week 2018 Jun 09:3351.

[16] Costa, Larissa Sampaio de Athayde, Pegler SP, Lellis RF, Krebs VLJ, Robertson S, Morgan T, et al. “Menkes disease: importance of diagnosis with molecular analysis in the neonatal period”. Revista da Associacao Medica Brasileira (1992) 2015 Sep;61(5):407-410.

[17] Fabio Agertt, Ana C.S. Crippa, Paulo J. Lorenzoni, Rosana H. Scola, Isac Bruck, Luciano de Paola, Carlos E. Silvado, Lineu C. Werneck. “Menkes Disease”. Arq Neuropsiquiatr 2007;65(1):157-160 2007.

[18] Walker FA, Goho C, Schanzer RB. “Menkes disease: report of two cases”. ASDC journal of dentistry for children 2002 Jan;69(1):70.

[19] Mohan A, Singh SK, Gupta AK, Pandey AK. “Menkes disease: Case report””. Pigment Int 2018;5:43-6.

[20] ETTA FRIEDMAN, ANN HARDEN, M. KOIVIKKO, AND G. PAMPIGLIONE. Menkes' disease: neurophysiological aspects”. Journal of Neurology, Neurosurgery, and Psychiatry, 1978, 41, 505-510 1978.